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Datasheet for the decision of 15 October 2024

Case Number: T 2130/22 - 3.3.07

Application Number: 18209003.5

Publication Number: 3470059

IPC: A61K9/00, A61K47/10, A61K47/32, A61K47/38, A61K9/14, A61K31/56, A61K31/573

Language of the proceedings: EN

Title of invention:
OPHTHALMIC SUSPENSION COMPOSITION

Patent Proprietor:
Bausch & Lomb Incorporated

Opponent:
Sandoz AG

Headword:
OPHTHALMIC SUSPENSION COMPOSITION/Bausch & Lomb Incorporated

Relevant legal provisions:
RPBA 2020 Art. 12(4), 12(6)
EPC Art. 83, 87(1), 56

Keyword:

Admission of a new document (No)
Main request - Sufficiency of disclosure (Yes)
Priority not valid
Main request - Inventive step (Yes)

Decisions cited:

G 0001/03

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Case Number: T 2130/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 15 October 2024

Appellant: (Opponent)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Patent Proprietor)	Bausch & Lomb Incorporated 1400 North Goodman Street, Area 62 Rochester, NY 14609 (US)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 20 July 2022 concerning maintenance of the European Patent No. 3470059 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

Summary of Facts and Submissions

I. European patent No. 3 470 059 was granted on the basis of a set of 15 claims .

Independent claim 1 as granted read as follows:

"1. An ophthalmic suspension comprising an ophthalmic active ingredient suspended in a formulation vehicle, wherein the ophthalmic active ingredient is loteprednol etabonate and is present as particles that have D_{v90} < 5 µm and D_{v50} < 1 µm, and the formulation vehicle comprises polycarbophil as a suspending agent, hydroxypropylmethyl cellulose as a non-ionic cellulose derivative, a poloxamer surfactant, glycerin, propylene glycol, and a borate buffer agent, and wherein the suspension is storage stable for at least one year."

II. The patent was opposed under Article 100 (a), (b), (c) EPC on the grounds that its subject-matter lacked an inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division finding that the patent in amended form meets the requirements of the EPC. The decision was based on the claims as granted as the main request and on auxiliary request 1 filed on 4 June 2021.

Auxiliary request 1 differed from the main request in the amended subject-matter of dependent claim 7.

IV. The documents cited during the opposition proceedings included the following:

D1: Phillips, E. et al, Investig. Ophthalmol. Vis. Sci. 2015, 56(7), abstract 1525;
D2: Cavet, M.E. et al, Investig. Ophthalmol. Vis. Sci. 2015, 56(7), abstract 1524;
D3: Schopf, L.R. et al., TVST 2015, 4(3), Article 11,1-12;
D4: Memon, A. et al., Int. J. Pharm. Biol. Arch. 2012, 4(1), 46-51;
D5: Coffey et al., Clin. Ophthalmol. 2013, 7, 299-312;
D6: Lakshmi, P. et al., Int. J. Pharm. Pharm. Sci. 2010, 2(S4), 35-40;
D7: Rajoria, G. et al., Am. J. PharmTech. Res., 2012, 2(4);
D8: Rowe, "Handbook of Pharmaceutical Excipients", 5th edition, Pharmaceutical Press, London, 2005, "Hypromellose";
D9: WO 2013/043387 A1;
D10: Press release of Bausch + Lomb entitled "Results positive for B+L sub-micron gel formulation of loteprednol etabonate", September 30, 2014;
D11: USP Monograph Poloxamer NF31;
D12: Schopf, L. et al., Ophthalmol. Ther. 2014, 3, 63-72;
D13: USP Monograph "Tyloxapol", 31 December 2012.

V. According to the decision under appeal, claims 7, 8, 14 and 15 of the patent as granted contravened Articles 100(c) and 76(1) EPC.

Auxiliary request 1 met the requirements of Articles 123(2), 76(1) and 83 EPC.

The priority document did not provide a basis for the claimed stability of at least one year, so that documents D1-D3 were prior art under Article 54(1) and (2) EPC.

D5 was the closest prior art, and the objective technical problem was the provision of a loteprednol etabonate (LE) formulation having improved efficacy while maintaining storage stability. The claimed solution was inventive over D5 alone or in combination with any of D2, D3 or D12.

VI. The opponent (hereinafter the appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal the appellant submitted the following item of evidence:

D14: Sepassi, S. et al., J. Pharm. Sci., 2007, 96(10), 2655-2666

VII. With its reply to the statement of grounds of appeal dated 4 April 2023, the patent proprietor (hereinafter the respondent) filed a main request corresponding to the request maintained by the opposition division, and 13 auxiliary requests.

Claim 1 of auxiliary request 1 was identical to claim 1 of the main request and to claim 1 as granted. Auxiliary request 1 differed from the main request in the addition of the feature "wherein the suspension is a gel" in dependent claim 7.

VIII. A communication from the Board, dated 21 June 2024, was sent to the parties.

IX. Oral proceedings took place on 15 October 2024. During the oral proceedings, the respondent withdrew the former main request such that auxiliary request 1 became the main request. In the present decision, auxiliary request 1 will be referred to as "the main request". The appellant had no further objections under Article 76(1) or 123(2) EPC against the claims of the main request.

X. The arguments of the appellant may be summarised as follows:

Admittance of D14 into the appeal proceedings

In its preliminary opinion, the opposition division considered that the alleged improvement on stability had not been shown over the whole scope of claim 1 and formulated the technical problem as the provision of an alternative suspension of LE (loteprednol etabonate), which was considered as a matter of normal experimental design and not inventive. In the appealed decision the opposition division surprisingly defined the objective technical problem more ambitiously, as “the provision of an LE formulation having improved efficacy while maintaining storage stability” and acknowledged the presence of an inventive step. D14 showed that for each grade of HPMC there was a minimum and a maximum necessary concentration to stabilize the active ingredient and that the problem linking particle size and stability was well known in the art.

In conclusion, D14 was filed as a direct reaction to the finding of the opposition division in the decision to maintain the opposed patent in amended form, was technically relevant and was a simple document showing

that it was not true that the problem as defined in the decision of the opposition division was unrecognized.

Main request - Sufficiency of disclosure

The skilled person is not taught how to perform the invention across the whole scope of the claim, i.e. using any grade and amount of HPMC, and still obtaining the claimed suspension "storage stable for at least one year".

Claim 11 was a second medical use claim directed to the ophthalmic suspension of claim 1 for use in treating an ophthalmic inflammatory condition. As the desired technical effect, i.e. the treatment of an ophthalmic inflammatory condition, was expressed in the claim, a problem of insufficient disclosure arose if said effect could not be achieved over the whole scope of the claim. This was actually the case since the skilled person was at a loss how to prepare the claimed formulations using any grade and/or amount of HPMC.

Validity of the priority

The validity of the priority was objected to in view of the claimed stability requirement and the excipients claimed in claim 1.

Main request - Inventive step

D5 did not disclose the particle size of LE, nor the presence of HPMC. The alleged effect of efficiency and storage stability had not been shown over the whole scope of claim 1. Therefore, the technical problem to be solved over D5 had to be formulated in a less ambitious manner, namely as the provision of an

alternative formulation of LE. The milling of loteprednol particles, preferably in the presence of the surfactant poloxamer, to obtain submicron particles was known from D2, D3, D4 and D12. Moreover, HPMC was a common excipient for ophthalmic formulations, as explained in handbook D8 and review article D6. The claimed subject-matter was not inventive for this reason.

D2, D3 and D12 were equally suitable starting points for the assessment of inventive step. None of these documents disclosed the detailed list of ingredients of the vehicle and D2 and D12 did not disclose the presence of a poloxamer surfactant. The patent explicitly taught that only a specific grade of HPMC in a specific minimum amount produced a stable formulation. Claim 1 was however not limited to such formulations. Therefore, the technical problem solved by claim 1 of the opposed patent was considered as the provision of an alternative formulation containing sub-micron particles of LE. The solution was obvious in light of the common general knowledge, illustrated by the teaching of D5, D7, D8 and D9.

XI. The arguments of the respondent may be summarised as follows:

Admittance of D14 into the appeal proceedings

The problem as defined by the opposition division in its decision was as posed in the patent and by the patentee, and could not be considered as a surprise. Moreover, D14 was not relevant technically, in particular since it related to a different technical teaching, namely it was about the production of nanoparticles.

Main request - Sufficiency of disclosure

The patent very clearly taught how to obtain the specified storage stability, such as in paragraph [0030], example 2 or example 6. No verifiable facts were provided, which would support the assertions of lack of sufficient disclosure.

Validity of the priority

The respondent gave as possible basis for the storage stability a statement on page 6 and the stability studies on pages 38-41 of the priority document. The formulation vehicle of claim 1 of the main request was specified in claim 7 of the priority document, in combination with the disclosure of the description on pages 10 and 11.

Main request - Inventive step

D5 was the closest prior art and the problem to be solved over D5 was the provision of a LE-containing ophthalmic composition, which provided an improved therapeutic efficacy, while at the same time providing a storage stable composition. In view of the examples, the problem was solved over the whole scope of the claims. In the path leading to improved efficacy, the present inventors were confronted with the challenges that submicron particles of LE in a polycarbophil formulation were surprisingly unstable. As shown in Example 2, an unexpected solution was found where such particles were stabilized in a matrix of polycarbophil and HPMC. The inventive contribution in relation to the closest prior art D5 (Lotemax®) was the realization that sub-micron LE particles had an increased

therapeutic efficacy and were rendered storage stable in a polycarbophil/HPMC matrix. The claimed solution was not obvious in view of any of the cited documents.

D2/D3/D12 were less promising starting points for assessing inventive step. The problem over these documents was the improvement in storage stability, and the claimed solution was not obvious in view of the cited documents.

XII. Requests

The appellant requested that the decision under appeal be set aside and that the patent be revoked. It also requested that D14 be admitted into the appeal proceedings.

The respondent requested that the decision under appeal be set aside and the patent be maintained according to one of auxiliary requests 1 (hereinafter the "main request") or 2-13 filed with letter dated 4 April 2023. It also requested that D14 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Admittance of D14 into the appeal proceedings

1.1 This document was filed by the appellant with its statement of grounds of appeal in support of its objections regarding sufficiency of disclosure and lack of inventive step; in particular it was filed in view of the definition of the problem by the opposition division in its decision, which, according to the appellant, constituted a surprise. The problem as defined by the opposition division in its preliminary

opinion was the provision of an alternative suspension of LE (loteprednol etabonate), which was considered as not inventive. In its decision, the opposition division defined the problem as the provision of an LE formulation having improved efficacy while maintaining storage stability, and acknowledged the presence of an inventive step. The opposition division further considered that "the prior art has not recognized the problem linking particle size and stability".

According to the appellant, D14 confirms that for each grade of HPMC a minimum and maximum concentration is required to stabilize drug nanoparticles (cf. D14, page 2660, right-hand column, second paragraph and Table 3).

1.2 The Board notes that document D14 is not a piece of evidence on which the decision under appeal was based. For this reason, its filing amounts to an amendment of the appellant's case and the Board has discretion to admit it pursuant to Article 12(4) RPBA.

Relevant criteria for the exercise of the Board's discretion are the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal and the need for procedural economy.

Moreover, the Board shall not admit evidence which should have been submitted in the proceedings leading to the decision under appeal (Article 12(6) RPBA).

1.3 In the present case, the Board notes that the problem as defined by the opposition division in its decision, namely the provision of an LE formulation having improved efficacy while maintaining storage stability, is the problem as defined in the patent (cf. for

instance par. [0001], [0010] [0030]-[0031]), and was also defended by the respondent during the entire opposition proceedings; hence, the decision of the opposition division reflects the patentee's position set out in its reply to the opposition dated 4 June 2021 and in its submissions dated 21 April 2022. The opponent could and should have reacted to this in due time. A change of the opinion of the opposition division during the oral proceedings based on known positions and opinions cannot constitute a surprise to any party.

Moreover, the information that for HPMC a minimum and maximum concentration is required is also provided in the contested patent (see in particular in example 2).

D14 also does not appear to be *prima facie* relevant. Indeed this document is directed to different active ingredients, namely nabumetone and halofantrine, having a different structure and a different solubility than LE. The formulation vehicle is completely different, since the compositions of D14 lack the association of polycarbophil with HPMC, which appears to be the core of the present invention and of the technical problem regarding the stability and the efficiency (see example 2, in particular par. [0067] of the specification). Furthermore, D14 relates mainly to the effect of the polymer molecular weight of HPMC on the mean particle size of the active ingredient during the milling process (Cf. Table 3 of D14), which is irrelevant to the present case. Consequently, the teaching of D14 cannot be applied to the present case and is irrelevant for the assessment of inventive step of the claimed invention.

1.4 Hence, D14 is not suitable to address the issues which led to the decision under appeal, which already speaks against its admittance. Moreover, the document was filed to counter arguments that were present since the beginning of the opposition proceedings. Therefore, it should have been filed during the opposition proceedings.

Consequently, the Board, exercising its discretion, does not admit document D14 into the appeal proceedings (Article 12(4) and 12(6) RPBA).

2. Main request - Sufficiency of disclosure

2.1 Claim 1 of the main request relates to a composition comprising qualitatively defined compounds, such as inter alia polycarbophil or HPMC, and is limited by the feature "storage stable for at least one year" which is a limiting functional feature. Thus, the skilled person must have been taught by the description how to prepare a composition "storage stable for at least one year", in particular which compounds to choose and in which amounts, to achieve the claimed technical effect.

2.2 The Board notes that the assessment of sufficiency of disclosure is made with reference to the application as a whole.

In the present case, the Table in paragraph [0043] gives the specific amounts of polycarbophil and HPMC, i.e. 0.1-0.5% by weight for both components, which are necessary to perform the claimed invention when LE is used as active agent. The description of the contested patent provides therein direct information and teaching with regard to the quantities of HPMC that provide stability.

The preferred grade of HPMC for stabilizing LE is further given in the Table of paragraph [0044] and in paragraph [0069]. Example 2 and Table 2 of the contested patent provide furthermore verifiable facts that the claimed suspension is not storage stable for at least one year, unless at least 0.05% HPMC E4M is used, and is not storage stable with 0.25% HPMC E3LV. This provides the skilled person with the guidance on how to adapt the concentration of the HPMC in relation to its grade. It appears indeed sufficient to increase the HPMC concentrations over the non-working examples given in Table 2 of example 2 to obtain a stabilising effect.

Example 6 confirms that the composition A according to the claimed invention is storage-stable for a two-year shelf life.

2.3 Consequently, the patent provides sufficient teaching for carrying out the claimed invention, in particular the subject-matter of the independent claims 1 and 11. The requirements of Article 83 EPC are therefore met.

3. Validity of the priority

The priority document mentions on page 6 a stability of two weeks, while the stability studies end after 8.5 months at 40°C. There is therefore no basis in the priority document for the claimed "wherein the suspension is storage stable for at least one year".

Moreover, the excipients of claim 1 of the main request, i.e poloxamer, glycerine, propylene glycol and borate buffer appear to represent selections among several possible alternatives disclosed on pages 10 and

11 of the priority document. Except for a very specific composition on page 5 of the priority document, there is no basis for the claimed combination of excipients.

Consequently, the priority of the present patent is not valid (Article 87 EPC) and D1, D2 and D3 are state of the art under Article 54(1) and (2) EPC.

4. Main request - Inventive step

4.1 The claimed invention relates to ophthalmic suspensions of loteprednol etabonate (LE) that are storage stable for at least one year. This means that the active agent will remain effectively suspended in the formation vehicle for this period of time without having to stir the packaged composition (cf. par. [0031] of the specification). This applies in particular to suspensions comprising sub-micron particles of LE in polycarbophil which are physically not stable and tend to aggregate over time, making it difficult or impossible to re-suspend the active ingredient, as would be needed for safe and effective administration to the eye (see par. [0067] of the specification). Moreover, the formulation provides a gel that, once instilled into the eyes gradually transforms into a liquid form (cf. par. [0030]).

4.2 The opposition division considered that D5 was the closest state of the art since it had the most features in common and disclosed a suspension formulation which inherently concerns the question of suspension stability. It considered that documents D2, D3, and D12 were less appropriate starting points for the assessment of inventive step.

The respondent shares the opinion of the opposition division with regard to the choice of D5 as the closest state of the art.

The appellant maintains that D2, D3 or D12 were equally promising starting points as D5.

4.2.1 D5 discloses a gel composition of loteprednol etabonate (LE) which is *inter alia* non-settling, eliminating the need to shake the product to resuspend the drug (see Abstract). A specific composition is given in table 2 on page 302 (see last column), which composition comprises 0.5% of LE without reference to any specific particle size, polycarbophil, glycerine, propylene glycol, boric acid, tyloxapol; **D5 does not disclose the particle size of LE and does not disclose the presence of HPMC.**

Table 2 is shown below:

Table 2 Comparison of 0.5% loteprednol etabonate suspension and gel formulations

Ingredients	Function	LE suspension 0.5%	LE gel 0.5%
Active substance			
Loteprednol etabonate	Steroid, anti-inflammatory	5.00 mg/mL	5.00 mg/g
Excipients			
Povidone	Suspending and/or viscosity-increasing agent	+	
Polycarbophil	Suspending and/or viscosity-increasing agent		+
Glycerin	Tonicity agent/humectant	+	+
Propylene glycol	Tonicity agent/humectant		+
Sodium chloride	Tonicity agent		+
Boric acid	Buffer/antimicrobial enhancer		+
Tyloxapol	Surfactant and/or wetting agent	+	+
Edetate disodium dihydrate	Chelant/antimicrobial enhancer	+	+
Benzalkonium chloride	Antimicrobial preservative	100 ppm	30 ppm
Sodium hydroxide and/or HCl	pH adjuster	qs to pH 5.5	qs to pH 6.5
Water for injection	Vehicle	qs to 1 mL	qs to 1 g

Note: The + sign indicates the presence of excipient in the formulation.
Abbreviations: LE, loteprednol etabonate; ppm, parts per million; qs, sufficient quantity.

D5 mentions that the concentration of LE suspended in the unshaken gel following 16 months of stability testing ranged from 100.4 to 107.6% and did not differ whether sampled near the top or near the bottom of the

bottled test samples (see page 303, right hand column, last paragraph).

4.2.2 D2 is an abstract disclosing a non-settling gel of 0.38% LE at sub-micron size. D2 indicates that the submicron particle size enhances the drug penetration to key ocular tissues (0.6 µm diameter). **This document does neither give any indication as to the composition, nor to its potential long term stability.**

4.2.3 D3 discloses the preparation of a LE formulation by nano-milling the crystalline drug in the presence of an MPP-enabling surface altering agent (mucus-penetrating particle). The agent is Pluronic F127, a poloxamer surfactant. The LE-MPP particles are composed by a drug core with a non-covalently attached poloxamer coating and have an average diameter of 240 to 350 nm. A 1% formulation was administered in the eyes of rabbits (see pages 2 and 3 of D3). **This document does not relate to a gel composition, does not disclose the claimed excipients (except poloxamer) and does not address the problem of stability.**

4.2.4 D12 discloses the use of a 0.4% formulation of LE-MPP particles which is formulated with excipients approved by the US FDA. The formulation is isotonic with a near neutral pH and contains 0.01% of benzalkonium chloride (see D12, page 65, left column). The composition shows an improved pharmacokinetic profile in the ocular tissue of rabbits (see Discussion) and was presented as chemically and physically shelf-stable at controlled room temperature (see page 65). **As for D3, this document does not relate to a gel composition and does not give any indication as to the composition or to the stability of the suspension.**

4.2.5 D2, D3 and D12 appear to be technically more remote from the claimed subject-matter than D5, and do not address the problem of storage stability. **The Board concurs therefore with the opposition division in the choice of D5 as closest prior art and that D2, D3 and D12 are less suitable starting points for the assessment of inventive step**; none of them disclose indeed explicitly a gel composition comprising polycarbophil and HPMC. The Board notes also that there is no evidence that the compositions disclosed in these documents are "storage stable for at least one year". Said documents do not even recognize the existence of a stability problem.

Nevertheless, in the following sections inventive step will be assessed first starting from D5, which is the subject of the appealed decision, but also starting from D2, D3 and D12, since these documents were considered as equally suitable starting points by the appellant.

4.3 D5 as closest prior art

4.3.1 The opposition division defined the problem over D5 as the provision of a LE formulation having improved efficacy while maintaining storage stability. The respondent agrees with this formulation of the problem (see letter of 4 April 2023, point 3.3)

The appellant considers that the problem is the provision of an alternative formulation of LE.

4.3.2 The respondent relies on Example 2, Table 2, as well on Example 4, in particular paragraphs [0087] to [0089] to show an effect on the therapeutic efficacy and storage

stability. The respondent also mentions Annex 1 in support of its arguments.

In Example 2, samples of 0.38% LE gel were prepared employing polycarbophil along with HPMC at different concentrations, or with other stabilizers or no stabilizer at all, and were bead-milled. The patent mentions that sub-micron particles of LE in a polycarbophil formulation are not physically stable and aggregate over time. It is explained that the polycarbophil polymer forms an open mesh type of structure that produces a shear thinning gel but allows unimpeded movement of particles within the matrix, while HPMC forms a more compact structure that can enhance the viscosity within the polycarbophil matrix, thereby reducing the particle movement and also inhibiting nucleation, thereby stabilizing the small particles by reducing the Ostwald ripening effect. Table 2 shows the stability of the size of sub-micron particles after 8.5 months at 40°C.

Table 2

	Stabilizer	Viscosity Enhancer	Nucleation inhibitor	VMD	Dv95
P	0.25% HPMC E4M	X	X	0.94	3.99
P	0.15% HPMC E4M	X	X	0.87	3.23
MP	0.05% HPMC E4M	X	X	1.23	3.48
NP	0.0006% HPMC E4M	X	X	2.68	12.33
NP	No Stabilizer			3.45	22.24
MP	0.25% HPMC E3LV		X	1.15	3.62
NP	0.25% CMC	X		3.33	19.47
NP	0.25% PVP	X		3.89	29.23
P	0.25% Soluplus		X	0.83	3.61
P = Protected MP = Moderately Protected NP = Unprotected					

Table 2 highlights that compositions comprising HPMC in a concentration comprised between 0.05% to 0.25% show a

better size stability than the compositions without stabilizer or with an alternative stabilizer. A composition comprising at the very low concentration of 0.0006% of HPMC is also shown to be ineffective. This example appears therefore to confirm the nucleation inhibiting and size stabilisation effect of HPMC in the presence of poylcarbophil polymer.

Annex 1 confirms the stability of the particle size over 36 months.

Example 4 makes a comparison between different compositions comprising LE with inter alia polycarbophil, but all without HPMC. Example 4 shows that micronized and sub-micronized compositions had an improved penetration in ocular tissues in comparison to the commercial product Lotemax, except for the tear fluid and the bulbar conjonctiva, which are not considered as target tissues (see par. [0088] and [0089], Tables 4.4-4.6).

4.3.3 The appellant considers that the alleged effect has not been shown over the whole scope of claim 1, in particular in view of example 2 and Table 2 of the patent. **The patent teaches indeed in paragraph [0069] that only a specific grade of HPMC in a specific minimum amount produces a stable formulation, while claim 1 is not limited to such formulations** (see also Table 2 of the specification). The appellant argues that it is not credible that all formulations falling within claim 1 exhibit an improved stability, irrespective of the vehicle which could be an oily vehicle not excluded from the scope of claim 1.

In the Board's view, this argument is irrelevant for the assessment of inventive step in the present case

for the following reasons. Claim 1 is limited by a functional feature in the form of a result to be achieved, namely "storage stable for at least one year", which is limitative and needs to be taken into account. When an effect is not expressed in a claim but is part of the problem to be solved, there can be a problem of inventive step. In the present case however, as the effect is part of the claim, it appears that in principle only an objection of insufficiency of disclosure can be raised (see G 1/03 point 2.5.2); however, as explained in point 2 above, the requirement of sufficiency of disclosure is met in the present case as the description provides guidance enabling the skilled person to ascertain how to obtain the desired stability.

4.3.4 In view of examples 2 and 4 of the patent, the existence of a technical effect has to be acknowledged and the problem is as defined by the respondent, namely the provision of a LE formulation having improved efficacy while maintaining storage stability.

The claimed solution is the presence of HPMC.

4.3.5 The appellant mentioned documents D2, D3, D4, D12, D6, and D8 with regard to the obviousness of the solution.

D5 itself does not provide the skilled person with the required teaching to solve the underlying objective technical problem. D5 only mentions HPMC in relation to a test vehicle for a short-term preclinical study with LE, but it does not teach or suggest that it can be used in a composition with further excipients.

Documents D2, D3 or D12 do not give any information with regard to the excipients used in the formulations

disclosed therein. They are in particular silent as to the possible presence of polycarbophil and in particular HPMC in the gel compositions. These documents might suggest that submicron size particles may lead to an improved efficiency, there is however no suggestion or teaching in these documents on how to improve or maintain efficacy while maintaining storage stability.

D4 suggests that LE particles may be milled and furthermore relates to a formulation comprising only LE, a surfactant and water and provides the skilled person neither with the motivation nor with the means to solve the objective technical problem.

HPMC is a known excipient for ophthalmic formulations as shown in D8 (page 346, right-hand column, third paragraph). D8 discloses that HPMC can be added as a thickening agent to vehicles for eye drops. D8 does however not relate to the improvement of therapeutic efficacy of ophthalmic active ingredients, let alone LE, or with the stabilization of nanoparticulate suspensions. The only conclusion that may be drawn from D8 is that HPMC is a known excipient and may be used in ophthalmic preparations. The same is however true for other compounds, such as carboxymethylcellulose or povidone, which failed to adequately stabilize the inventive compositions (cf. Table 2 of the patent). Consequently, D8 cannot render obvious the claimed subject-matter.

D6 mentions the cellulosic polymers in general as stabilizers in particular to prevent Ostwald's ripening and agglomeration of nanosuspension. HPMC is not specifically mentioned (see page 37 "Stabilizers"); D6 mentions several possibilities as stabilizer, such as

poloxamer, polysorbate, povidone or particular lecithin. D6 does not suggest that HPMC is a suitable agent for stabilizing the claimed composition, and does neither suggest the association of HPMC with polycarbophil. Consequently, D6 cannot render obvious the claimed subject-matter.

4.3.6 Consequently, the claimed solution is not obvious and the main request is inventive over D5 in combination with any of the documents D2, D3, D12, D6, and D8.

4.4 D2, D3 or D12 as closest prior art

4.4.1 According to the appellant, the only difference between the disclosure of D2/D3/D12 and claim 1 of the opposed patent is the list of excipients. In the written proceedings, the appellant defined the problem as the provision of an alternative formulation containing sub-micron particles of loteprednol etabonate, while during the oral proceedings, the appellant agreed that it was the provision of a composition of LE with improved stability.

The respondent defines the problem in the same way, namely as the provision of a formulation containing sub-micron particles of LE with an improved storage stability.

4.4.2 The claimed solution is the formulation vehicle comprising polycarbophil as a suspending agent, hydroxypropylmethyl cellulose as a non-ionic cellulose derivative, a poloxamer surfactant (in view of D2 and D12), glycerin, propylene glycol, and a borate buffer agent.

The problem is considered to be solved for the same reasons as above (see point 4.3.2). Thus, the technical problem to be solved is the provision of a formulation containing sub-micron particles of LE with an improved storage stability.

4.4.3 The appellant considers the solution obvious in the light of the common general knowledge, as supported by documents D5, D6, D7, D8 and D9.

In D2, a non-settling gel with submicron particles of loteprednol etabonate is compared with the commercial Lotemax® gel containing micron particles of the active ingredients. The appellant argues that the skilled person would have expected that said submicron particles could be formulated in a composition very similar to the one of Lotemax® gel. The composition of Lotemax® gel is known from D5, is stable at least one year and is very similar to the claimed composition (cf. D5 Table 2 and page 303). The skilled person would have to simply add HPMC, which was known from further documents D6 or D8 (see above).

D7 discloses on page 37 that hydroxypropyl methylcellulose and methylcellulose were combined with carbopol to increase the viscosity of the gels and to reduce the concentration of the incorporated carbopol.

D9 discloses in Table 2 on page 19, a suspension formulation of LE, comprising a carbopol, propylene glycol, glycerin, edetate disodium dihydrate, tyloxapol, boric acid, sodium chloride and BAK.

4.4.4 The Board disagrees with the appellant's arguments and conclusions regarding obviousness in view of D2, D5, D6, D7, D8 and D9 . In the Board's view, the facts and

arguments with regard to the presence of HPMC as a technical difference, as already explained under points 4.3.4 above, equally apply to these documents. There is no incentive in any of the cited documents to make any changes to their compositions in order to solve a problem of stability which was not even recognized in documents D2, D3 or D12. There is no incentive in any of the cited documents to add HPMC in order to improve the stability of a gel comprising LE containing the polymer polycarbophil. The disclosure of these documents cannot render the claimed solution obvious.

4.4.5 Consequently, the claimed solution is not obvious and the main request is inventive also when starting from D2, D3, or D12 as the closest prior art.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the claims according to the main request, filed as auxiliary request 1 with letter dated 4 April 2023, and a description to be adapted thereto if necessary.

The Registrar: The Chairman:

A. Vottner A. Usuelli

Decision electronically authenticated